

- hyper-responsiveness. *J Allergy Clin Immunol.* 2020;11:S0091-S96. <https://doi.org/10.1016/j.jaci.2020.03.046>
9. Pujols L, Mullol J, Alobid I, Roca-Ferrer J, Xaubet A, Picado C. Dynamics of COX-2 in nasal mucosa and nasal polyps from

aspirin-tolerant and aspirin-intolerant patients with asthma. *J Allergy Clin Immunol.* 2004;114(4):814-819.

DOI: 10.1111/all.14616

Assessing the protective role of allergic disease in gastrointestinal tract cancers using Mendelian randomization analysis

To the Editor,

Immune hypersensitivity featured among allergic individuals has been proposed to enhance immune surveillance, thereby inhibiting

abnormal cell growth and thus reduce cancer risk.^{1,2} Similarly, the prophylaxis theory suggests that allergy symptoms may prevent cancer development by removing potential carcinogens.² This hypothesis

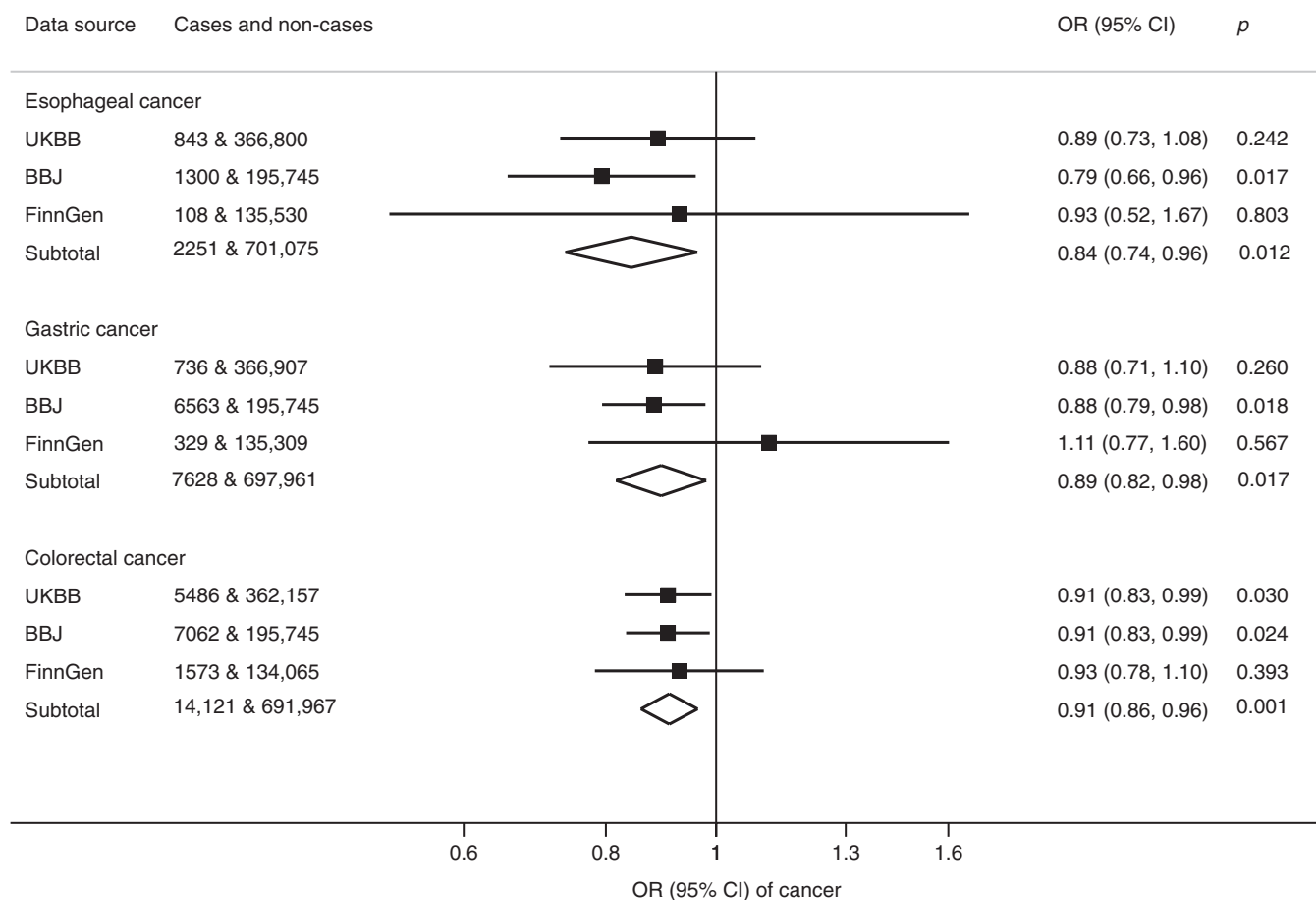


FIGURE 1 Associations of genetic predisposition to allergic disease with esophageal, gastric, and colorectal cancer. BBJ, indicates BioBank Japan; CI, confidence interval; OR, odds ratio; UKBB, UK Biobank

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *Allergy* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd

TABLE 1 Associations of genetic predisposition to allergic disease with esophageal, gastric, and colorectal cancer in sensitivity analyses

	Esophageal cancer			Gastric cancer			Colorectal cancer		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
UK Biobank									
IVW-fixed effects method	0.89	0.73, 1.08	.242	0.88	0.72, 1.09	.253	0.91	0.84, 0.98	.015
Weighted median method	0.92	0.69, 1.23	.571	0.84	0.61, 1.15	.270	0.96	0.84, 1.08	.489
MR-Egger regression	1.01	0.6, 1.68	.976	1.23	0.71, 2.13	.468	0.91	0.73, 1.15	.442
MR-PRESSO method ^a	n/a	n/a	n/a	n/a	n/a	n/a	0.90	0.83, 0.98	.012
Heterogeneity ^b	$I^2 = 0\%$; Cochrane's Q = 114; $P_{\text{het}} = .877$			$I^2 = 0\%$; Cochrane's Q = 137; $P_{\text{het}} = .393$			$I^2 = 21\%$; Cochrane's Q = 168; $P_{\text{het}} = .021$		
Pleiotropy ^c	Intercept = -0.007 ; $P_{\text{pleiotropy}} = .601$			Intercept = -0.018 ; $P_{\text{pleiotropy}} = .208$			Intercept = 0.000 ; $P_{\text{pleiotropy}} = .944$		
BioBank Japan									
IVW-fixed effects method	0.79	0.66, 0.96	.017	0.88	0.81, 0.96	.004	0.91	0.83, 0.99	.022
Weighted median method	0.65	0.49, 0.86	.003	0.94	0.82, 1.07	.332	0.87	0.76, 0.99	.034
MR-Egger regression	0.65	0.37, 1.14	.130	0.83	0.61, 1.13	.237	0.84	0.66, 1.08	.181
MR-PRESSO method ^a	n/a	n/a	n/a	0.93	0.84, 1.02	.138	n/a	n/a	n/a
Heterogeneity ^b	$I^2 = 0\%$; Cochrane's Q = 92; $P_{\text{het}} = .833$			$I^2 = 31\%$; Cochrane's Q = 154; $P_{\text{het}} = .002$			$I^2 = 3\%$; Cochrane's Q = 109; $P_{\text{het}} = .407$		
Pleiotropy ^c	Intercept 0.011; $P_{\text{pleiotropy}} = .453$			Intercept = 0.003 ; $P_{\text{pleiotropy}} = .682$			Intercept = 0.004 ; $P_{\text{pleiotropy}} = .541$		
FinnGen consortium									
IVW-fixed effects method	0.93	0.52, 1.67	.803	1.11	0.79, 1.56	.537	0.93	0.79, 1.09	.352
Weighted median method	0.79	0.34, 1.85	.586	1.21	0.72, 2.02	.477	1.11	0.88, 1.4	.38
MR-Egger regression	0.30	0.06, 1.43	.129	1.00	0.37, 2.67	.999	0.88	0.55, 1.39	.578
MR-PRESSO method ^a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Heterogeneity ^b	$I^2 = 0\%$; Cochrane's Q = 81; $P_{\text{het}} = .998$			I^2 14%; Cochrane's Q 140; $P_{\text{het}} = .103$			I^2 16%; Cochrane's Q 143; $P_{\text{het}} = .078$		
Pleiotropy ^c	Intercept = 0.061 ; $P_{\text{pleiotropy}} = .127$			Intercept 0.006 ; $P_{\text{pleiotropy}} = .818$			Intercept 0.003 ; $P_{\text{pleiotropy}} = .797$		

^aThere was no corrected estimate (n/a) if no outlier was identified. One outlier was identified and removed in the analysis of colorectal cancer based on UK Biobank (P value for the distortion test was .815) and two outliers were identified and removed in the analysis of gastric cancer based on Biobank Japan (P value for the distortion test was .137).

^bWe observed significant heterogeneity among used SNPs in the analysis of colorectal cancer based on UK Biobank and gastric cancer based on Biobank Japan ($P_{het} < .05$).

^cPleiotropy was measured by the intercept from MR-Egger regression. Pleiotropy was not detected in any analysis (all $P > .05$).

envisages a preventive role specifically for cancers of tissues that interface with the external environment, such as gastrointestinal tract cancers.² A reduced risk of gastrointestinal tract cancer among individuals with self-reported allergic conditions has been observed in several but not all observational studies.^{3,4} However, whether the associations are causal remains unclear as observational studies are prone to residual confounding. Therefore, we conducted a Mendelian randomization study⁵ to determine the causal role of genetic liability to allergic disease in esophageal, gastric, and colorectal cancers.

One hundred and thirty-six single-nucleotide polymorphisms (SNPs) associated with at least one allergic disease (asthma, allergic rhinitis, or eczema) at $P < 3 \times 10^{-8}$ in 180 129 cases and 180 709 non-cases of European ancestry were considered as instrumental

variables.⁶ The 136 SNPs were independent and not in linkage disequilibrium defined by distance >1 Mb and $r^2 < 0.02$. The SNPs explained around 2.6% of phenotypic variance. Summary-level data for the associations of those SNPs with esophageal, gastric, and colorectal cancers were obtained from the UK Biobank, BioBank Japan, and FinnGen consortium. The main analysis was based on the multiplicative random-effects inverse-variance weighted method, and estimates from the different studies were combined using fixed effects meta-analysis. The inverse-variance weighted method under a fixed effects model and the weighted median, MR-Egger regression, and MR-PRESSO methods were employed as sensitivity analyses. The I^2 (%) statistic and Cochrane's Q value were calculated to assess heterogeneity among estimates of individual SNPs. We considered

associations with P values below .017 (where $P = .05/3$) to represent strong evidence of causal associations and associations with P values below .05 but above .017 as suggestive evidence of associations.

Genetic liability to allergic disease was associated with lower risk of the gastrointestinal tract cancers in the meta-analysis of UK Biobank, BioBank Japan, and FinnGen, though the association with gastric cancer was not statistically significant after correcting for multiple testing (Figure 1). The combined odds ratio was 0.85 (95% confidence interval, 0.75, 0.97; $P = .016$) for esophageal cancer, 0.90 (95% confidence interval, 0.82, 0.98; $P = .020$) for gastric cancer, and 0.91 (95% confidence interval, 0.86, 0.96; $P = .001$) for colorectal cancer for one unit increase in log-transformed odds of allergic disease. The associations were consistent across data sources with the exception of the estimate for gastric cancer in FinnGen which was above one but with a broad confidence interval that overlapped the estimates in UK Biobank and BioBank Japan. Results were consistent in sensitivity analyses for all three cancer outcomes (Table 1).

A potential limitation arises from the fact that we used an instrument for liability to allergic disease that was developed using genetic data from individuals of European ancestry and applied to a Japanese population. However, a consistent effect of risk alleles of SNPs for allergic disease on asthma in BioBank Japan indicates a high validity of used instrumental variables and a negligible population bias. In addition, a robust pattern of established associations in both Asian and European populations suggested that the associations were portable across populations of distinct ancestries. A further limitation of this work is that we cannot make specific inferences about the impact of food allergies on cancer risk.

In summary, this MR study supports a protective effect of allergic disease against esophageal and colorectal cancer and possibly gastric cancer. This finding may be useful for further laboratory studies to understand the immunological pathways involved in gastrointestinal tract carcinogenesis.

ACKNOWLEDGMENTS

Genetic instruments for allergic disease were obtained from a published meta-analysis of genome-wide association studies.⁶ Genetic association estimates for esophageal, gastric, and colorectal cancers were obtained from the UK Biobank study, BioBank Japan, and FinnGen consortium. The authors thank all investigators for sharing these data. Analyses of UK Biobank data were performed under application 29202.

CONFLICT OF INTEREST

Dr. Mason reports grants from the EC-Innovative Medicines Initiative (BigData@Heart) and the National Institute for Health Research (Cambridge Biomedical Research Centre at the Cambridge University Hospitals NHS Foundation Trust).

ETHICAL APPROVAL

All studies included in cited genome-wide association studies had approved by a relevant review board. The present MR analyses were approved by the Swedish Ethical Review Authority (2019-02793).

FUNDING INFORMATION

SK is supported by a Cancer Research UK program grant, the Integrative Cancer Epidemiology Programme (C18281/A19169). AMM is supported by EC-Innovative Medicines Initiative (BigData@Heart). SB is supported by Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (204623/Z/16/Z). SCL is supported by research grants from the Swedish Research Council for Health, Working Life and Welfare (Forte; grant no. 2018-00123), the Swedish Research Council (Vetenskapsrådet; grant no. 2019-00977), and the Swedish Heart-Lung Foundation (Hjärt-Lungfonden; grant no. 20190247). This work is supported by funding from the National Institute for Health Research (to SB) [Cambridge Biomedical Research Centre at the Cambridge University Hospitals NHS Foundation Trust] [*]. *The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Shuai Yuan¹ 

Mathew Vithayathil²

Siddhartha Kar³

Paul Carter⁴

Amy M. Mason^{5,6}

Shao-Hua Xie⁷

Stephen Burgess^{4,8}

Susanna C. Larsson^{1,9} 

¹Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

²MRC Cancer Unit, University of Cambridge, Cambridge, UK

³MRC Integrative Epidemiology Unit, Bristol Medical School, University of Bristol, Bristol, UK

⁴Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

⁵British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

⁶National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge and Cambridge University Hospitals, Cambridge, UK

⁷Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

⁸MRC Biostatistics Unit, University of Cambridge, Cambridge, UK

⁹Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Correspondence

Susanna C. Larsson, Institute of Environmental Medicine, Karolinska Institutet, Nobelsväg 13, Stockholm, 17177, Sweden; Department of Surgical Sciences, Uppsala University, Dag Hammarskjölds Väg 14B, Uppsala, 75185, Sweden.

Email: susanna.larsson@ki.se

ORCID

Shuai Yuan  <https://orcid.org/0000-0001-5055-5627>Susanna C. Larsson  <https://orcid.org/0000-0003-0118-0341>

REFERENCES

1. Rigoni A, Colombo MP, Pucillo C. Mast cells, basophils and eosinophils: from allergy to cancer. *Semin Immunol.* 2018;35:29-34.
2. Sherman PW, Holland E, Sherman JS. Allergies: their role in cancer prevention. *Q Rev Biol.* 2008;83(4):339-362.
3. D'Arcy M, Rivera DR, Grothen A, Engels EA. Allergies and the subsequent risk of cancer among elderly adults in the United States. *Cancer Epidemiol Biomarkers Prev.* 2019;28(4):741-750.

DOI: 10.1111/all.14619

Chronic exposure to benzo(a)pyrene-coupled nanoparticles worsens inflammation in a mite-induced asthma mouse model

To the Editor,

Asthma is a highly prevalent chronic inflammatory disease of the airways characterized by airway hyperresponsiveness (AHR) and mucus hyperproduction. In the last decades, asthma has been affecting approximately 20% of the population worldwide and genetic changes alone cannot explain this rapid increase. During the same period, increased vehicular traffic and other combustion processes have resulted in a significant increase in ambient particle matter (PM) that can bind polycyclic aromatic hydrocarbons (PAHs) on their surface. PAHs from diesel exhaust and other sources were shown to play a role in the exacerbation of allergic immune responses in humans.¹ In acute asthma models, co-exposure to the PAH, benzo(a)pyrene (B(a)P), and ovalbumin enhances the production of allergen-specific IgE, systemic Th2 response, and airway inflammation in mice.²

Nanoparticles ($\leq 0.1 \mu\text{m}$), that represent only 2.3% of total PM mass, contribute to 23-30% of the PAHs alveolar deposition coming from roadside sources. Moreover, their small size allows evading clearance from the lung, leading to long-term retention.³ This suggests that nanoparticles are significant contributors of PAHs deposition in the lung and thus, may contribute to acute and chronic inflammation. However, few studies have evaluated the impact of chronic exposure to this pollutant on allergic asthma. Therefore, we established a murine allergic asthma model using the house dust mite (HDM) allergen, to explore the impact of chronic exposure to nanoparticles coupled to PAHs on airway inflammation (Figure S1A for exposure model). In this study, we used carbon black nanoparticles from printers uncoated as reference (NP-Ø) and B(a)P-coated (NP-B(a)P) as a model of nano-particulate pollutant.

We analyzed the effects of chronic exposure to NP-B(a)P on different asthma parameters. As expected, exposure to HDM-induced

allergic asthma including increased AHR (Figure S1B), HDM-specific IgE, and IgG1 in sera (Figure S1C) and pulmonary inflammation, characterized by elevated total cell numbers in the broncho-alveolar lavage (BAL) composed of eosinophils, neutrophils, lymphocytes, and macrophages compared to PBS control mice (Figure 1A). Moreover in this model, we did not observe airway remodeling (data not shown). Neither NP-Ø nor NP-B(a)P nanoparticles alone induced airway inflammation. However, NP-B(a)P but not NP-Ø increased AHR in non-sensitized mice, suggesting that B(a)P has a specific effect on AHR independently of HDM. In HDM-sensitized mice, HDM-induced AHR was abolished by NP-Ø and decreased by NP-B(a)P although this one remained increased compared to the PBS control group (Figure S1B). Surprisingly, both nanoparticles co-exposed with HDM did not modify inflammatory cell recruitment in the BAL (Figure 1A) and did not induce bronchial remodeling (data not shown). However, this result was not supported by cellular infiltration of lung tissue as shown by hematoxylin and eosin histological stain (Figure S1D) and total lung single cell suspension (Figure 1B). Indeed, increased total cell numbers were enhanced in the lungs of HDM + NP-B(a)P mice compared to HDM-sensitized mice (Figure 1B). This cellular infiltration was mainly due to a significant increase of eosinophils, Ly6C⁺ monocytes/macrophages, and CD4⁺ T cells in HDM-sensitized mice compared to the PBS group (Figure 1B). Interestingly, NP-B(a)P significantly modifies the HDM-induced cell recruitment. Indeed, Ly6C⁺ as well as Ly6C⁺ monocytes/macrophages were significantly elevated in HDM + NP-B(a)P compared to HDM-sensitized mice. Moreover, neutrophils, NKT-like cells and CD8⁺ T cells, not recruited in HDM-sensitized mice, were significantly increased in lungs from HDM + NP-B(a)P mice (Figure 1B). NKT-like cells differ from classical NKT by recognizing antigen presented through major histocompatibility complex and not through CD1d,